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# Genetic Polymorphism Of The System Of Natriuretic Peptides And Long-Term Results Of Coronary Artery Stenting

Daminov Botir Pulatovich, Alyavi Bakhrom Ansixonovich,
Azizov Shukhratjon Ismatdjonovich
*Tashkent Pediatric Medical Institute, Tashkent*

***ABSTRACT***

***The aim of the study*** *was to determine the effect of genetic polymorphism on the effects of endovascular revascularization in patients with coronary artery disease, angina pectoris FC III-IV*

***Materials methods.*** *The study included 158 patients with coronary heart disease with angina pectoris of FC III-IV tension (women 34 - 21.52%). Upon inclusion in the study, all patients underwent: Echocardiography, TLC, genotyping of 6 genes of the system of natriuretic peptides, coronary angiography and stenting of the coronary arteries. For follow-up examination, patients were invited after a year. The study included echocardiography, TLC, stress echocardiography.*

***Results.*** *Genetic analysis allows predicting the long-term effect of coronary artery stenting: the relative risk of coronary heart disease progression (in the form of stress-induced ischemia) in patients with minor alleles is 2.12 times higher than in patients with dominant homozygotes for genes of the natriuretic peptide system.*

***Conclusion.*** *The present study found that the presence of minor alleles of genes of the system of natriuretic peptides is associated with a greater prevalence of atherosclerotic lesions of the coronary bed, the activity of structural and functional remodeling of the heart. In addition, the presence of minor alleles reduces the long-term effectiveness of coronary revascularization, both in the aspect of coronary atherosclerosis and in the aspect of the functional state of the myocardium (progression of LV dilatation and preservation of the hibernating myocardium).*

***KEY WORDS:*** *stenting of coronary arteries, sodium urotic peptides, genetic polymorphism, stress echocardiography*

## INTRODUCTION

Coronary heart disease is still the leading cause of death among adults in many developed countries (7 million a year). In the United States, about 1 million deaths from coronary heart disease are recorded annually, of which approximately 160,000 are people 65 years of age or younger [1]. 650 000 Europeans die every year from coronary heart disease, and AMI causes the death of approximately 420 000 people [2].

After AMI, many patients are characterized by the presence of symptoms of angina pectoris, impaired functional state and a decrease in the quality of life. The progressive nature of stenosing atherosclerosis, the need to reduce high mortality, improve the quality of life and increase the level of social rehabilitation of patients are a powerful incentive for finding new ways to effectively treat the disease. The introduction of interventional treatments has become a new page in the treatment of coronary artery disease.

Among the complex lesions of CA, chronic occlusion is one of the most common and occurs in approximately 15% of patients referred for coronary angiography. Restoring the patency of the spacecraft with the use of percutaneous coronary interventions can reduce the severity of angina pectoris, increase the contractile function of the myocardium and improve the prognosis. Comparison of patients with successful and unsuccessful PCI shows that the quality of life and prognosis for successful intervention are significantly better [3,4].

It is known that cardiovascular diseases are multifactorial pathological conditions based on complex pathogenesis that determines the formation of a phenotype based on the interaction of genetic factors with modifiable environmental factors. Understanding the role of genetic factors in the development and progression of heart failure allows you to take a fresh look at the etiology and pathogenesis of this disease. Finally, the genetic studies currently available for cardiological practice make it possible to objectively evaluate the prospects and effectiveness of treatment, thereby opening up new possibilities for pharmacogenetics and pharmacogenomics that can provide improved quality

of life and survival of patients with heart failure [5,6]. More and more evidence shows that specific genetic factors can lead to a change in properties in the LLP gene system, which affect the risk of cardiovascular disease and / or the response to drug treatment.

The aim of the study was to determine the effect of genetic polymorphism on the effects of endovascular revascularization in patients with coronary artery disease, angina pectoris FC III-IV.

## MATERIALS AND METHODS

The study included 158 patients with coronary heart disease with angina pectoris of FC III-IV tension (women 34 - 21.52%). The average age of patients is 55.86 ± 9.08 years. All patients underwent coronary angiography and only patients with indications for stenting of the coronary arteries were included in the study. The study and revascularization were carried out on the basis of the Department of Interventional Cardiology of the RSSPCT and M. N. Semashko MR of the Ministry of Health of the Republic of Uzbekistan. The study did not include patients with atrial fibrillation, acute febrile diseases, end-stage organ failure, diseases of other organs and systems requiring constant basic therapy, patients with diabetes mellitus and thyroid diseases, malignant neoplasms, patients with contraindications for endovascular revascularization (ulcerative processes in Gastrointestinal tract, hemorrhagic diathesis, chronic kidney disease with an estimated glomerular filtration rate of less than 60 ml / min), patients with intolerance to iodine-containing contrast agents, patients who refused the endovascular procedure for personal reasons.

Among patients included in the study, 48 patients (30.38%) had post-infact cardiosclerosis. In the remaining patients, there was no anamnestic and electrocardiographic signs of myocardial infarction.

At the time of inclusion in the study, all patients were taking standard basic therapy, including:
- antiplatelet therapy: aspirin - 152 patients (96.20%), clopidogrel - 6 patients (3.80%);
- lipid-lowering therapy: rosuvastatin 10-20 mg / day - 23 patients (14.56%), atorvastatin 20 mg / day - 82 patients (51.90%);
- beta-blocker (bisoprolol, metoprolol, nebivolol) - 142 patients (89.88%);
- calcium channel blocker: verapamil 240 mg / day - 12 patients (7.59%), amlodipine - 46 patients (29.11%);
- angiotensin converting enzyme inhibitors (enalapril, rimipril, perindopril, lisinopril) - 64 patients (40.51%);
- angiotensin II receptor blocker (valsartan, losartan, telmisartan) - 28 patients (17.72%);
- antiarrhythmics (amiodarone) - 27 patients (17, 09%);
- diuretics (furosemide, torasemide, spironolactone) - 49 patients (31.01%);
- isosorbide mono / dinitrate - 142 patients (89.88%).

Upon inclusion in the study, all patients underwent: Echocardiography, TLC, genotyping of 6 genes of the system of natriuretic peptides, coronary angiography and stenting of the coronary arteries. After the procedure, patients were given recommendations on basic therapy (double antiplatelet therapy, rosuvastatin 20 mg / day, beta-blocker / calcium channel blocker in case of contraindications to beta-blockers in individually selected doses, angiotensin converting enzyme inhibitors / angiotensin antagonistin antagonistin receptor inhibitors in the case of antiarrhythmics, diuretics and nitrates according to indications) and the direction for observation by a cardiologist at the place of residence.

For follow-up examination, patients were invited after a year. The study included echocardiography, TLC, stress echocardiography.

During statistical processing, intergroup comparisons of the structural and functional state of the heart before revascularization and in the long term (1 year) and differences in the relative dynamics of the indicators were studied.

### Echocardiography

Echocardiography was carried out on an ultrasound scanner ..... equipped with a convex cardiological sensor with a frequency of 2-4 MHz. The study was conducted lying on the left side and on the back. Scanning was carried out using standard echocardiography positions and projections. The following parameters were determined:

- final diastolic volume of the left ventricle;
- LV ejection fraction (EF);
- sphericity index;

- Index of violation of regional contractility;
- index of systolic myocardial remodeling;
- e '/ a' ratio of the rates of diastolic displacement in the phase of the early and late diastole of the lateral edges of the mitral (for LV) and tricuspid (for pancreas) valves;
- LV myocardial mass index (LVMI);
- Tei- integral index of the functioning of the ventricular myocardium;
- The right ventricle (pancreas);
- systolic pressure in the pulmonary artery
- Pressure jamming in the pulmonary artery;
- TAPSE - degree of apical systolic displacement of the lateral edge of the tricuspid valve ring.

**Stress Echocardiography** study was performed with dynamic physical activity using the TMT method, Bruce profile, stage duration - 3 minutes. During the test, the dynamics of the ejection fraction and the index of violation of regional contractility were studied. The sample was interpreted as the presence of stress-induced ischemia in the event of ECG or clinical criteria for ischemia, a decrease in the ejection fraction, or an increase in the index of violation of regional contractility. The hibernating myocardium was diagnosed on the basis of a decrease in the index of violation of regional contractility against the background of the load. The normal result is an increase in the ejection fraction against the background of the load without changing the index of violation of regional contractility.

Six-minute walk test. The patient was asked to walk at the fastest pace for 6 minutes. In the event of a stop, time counting continued. Estimated distance traveled.

**The study of gene polymorphisms** was carried out at the high technology center of the Academy of Sciences of the Republic of Uzbekistan under the leadership of Turdikulova Sh.U. in the biology laboratory. Genotyping was carried out by polymerase chain reaction (PCR). To study single nucleotide mutations (SNPs), 6 polymorphisms were selected. The presence of minor alleles and allelic genotypes of 6 SNP genes NPPA and NPPB was determined

All received data was entered into Excell summary tables. After the formation of the groups, all parameters were described in the form of the arithmetic mean and its standard deviation. The reliability of intergroup differences was determined using Student's criterion. In the case of multiple comparisons, the Student criterion was corrected by the Bonferroni correction. A comparison of the frequency of occurrence of signs between groups was carried out using the tabular Chi-square criterion and checking its reliability according to the tables depending on the number of degrees of freedom.

## RESULTS AND DISCUSSION

Given the low frequency of occurrence of minor alleles during the study (Fig. 1), we developed a scale for assessing genetic polymorphism (Table 1), according to which a patient was assigned 1 point for each homozygous dominant genotype, 2 points for each heterozygous genotype, each homozygous minor phenotype - 3 points, that is, a scoring characterizes the presence and number of minor alleles. The sum of scores for all 6 loci determined the scoring of genetic polymorphism for 6 genes of the system of natriuretic peptides. The vast majority of patients in this study showed a score of 6 (113 people - 71.52%), in 45 patients (28.48%), the score was higher, indicating the presence of minor alleles (Fig. 2).

**Table 1. Scale of genetic polymorphism. Studied allelic SNP genotypes of the NPPA and NPPB genes in the study group and their frequency (%)**

| SNP | Homo-zygotic Dominant Allele | Score | Hetero-zygotic allele | Score | Homo-zygotic minor allele | Score |
|---|---|---|---|---|---|---|
| rs5068 | CC 94,94% | 1 | CT 5,06% | 2 | TT 0% | 3 |
| rs198388 | CC 94,30% | 1 | CT 4,43% | 2 | TT 1,27% | 3 |
| rs198389 | TT 94,30% | 1 | TC 5,70% | 2 | CC 0% | 3 |
| rs5065 | CC 89,87% | 1 | TC 8,23% | 2 | TT 1,90% | 3 |
| rs632793 | AA 98,10% | 1 | AG 1,90% | 2 | GG 0% | 3 |
| rs198358 | AA 89,87% | 1 | AG 10,13% | 2 | GG 0% | 3 |

Polymorphism score = total points for all 6 genes

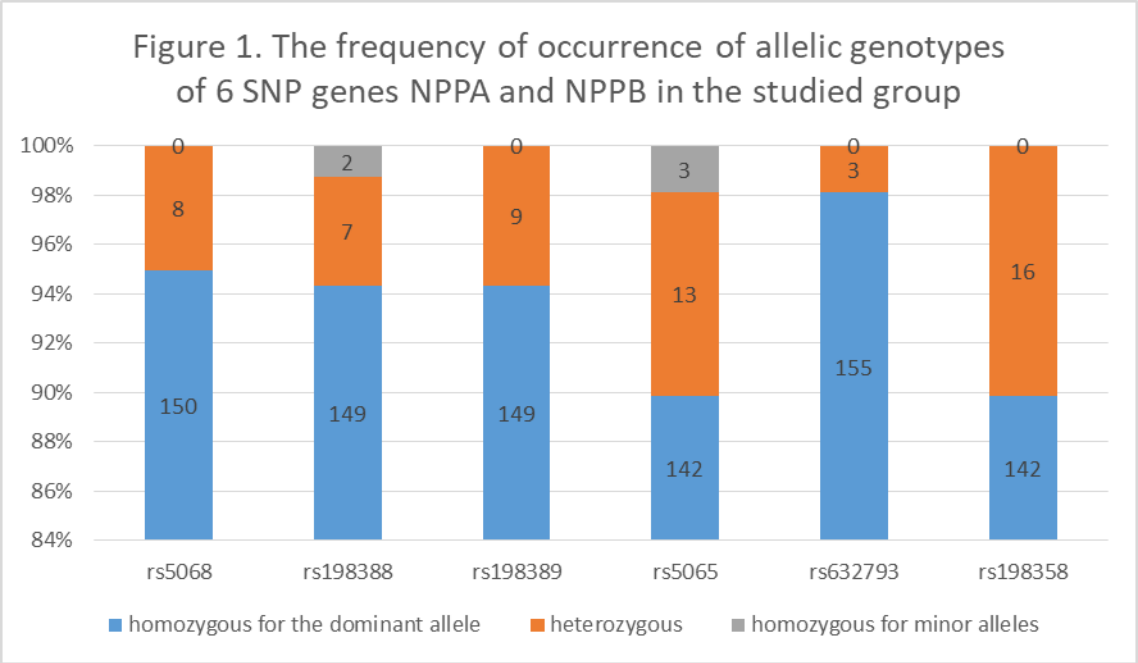



Figure 1. The frequency of occurrence of allelic genotypes of 6 SNP genes NPPA and NPPB in the studied group

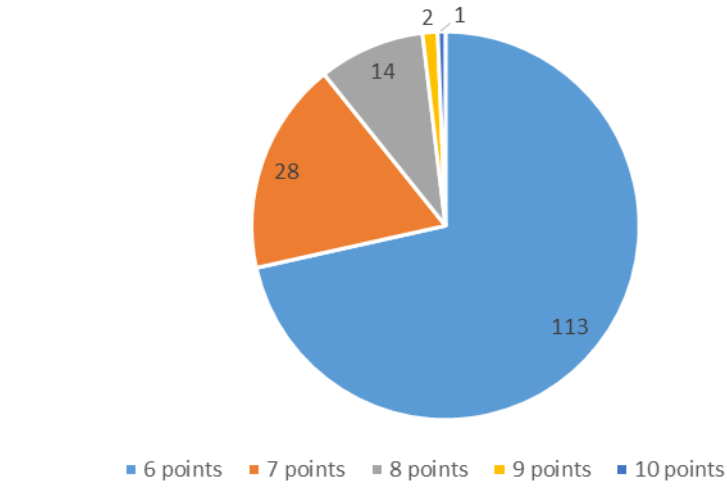



Figure 2. Frequency of occurrence of different points of genetic polymorphism in patients with angina pectoris FC III-IV

To study the effect of genetic polymorphism on the delayed results of endovascular coronary revascularization, all patients included in the study were divided into 2 groups: patients with a graded assessment of genetic polymorphism by 6 genes of the uretic peptide system 6, i.e. dominant homozygotes (113 patients) and with a ball a score higher than 6 points, that is, having at least 1 minor allele of the studied SNPs (45 patients). Comparison of these groups of patients showed that by age these groups did not differ from each other (Table 2).

Coronaroangiography revealed that the presence of minor alleles was associated with a significantly more pronounced lesion of the coronary bed: the number of hemodynamically significant stenoses of the coronary arteries was significantly higher in the group of patients with a high score of genetic polymorphism ($p < 0.001$).

Comparison of the echocardiographic parameters revealed that the presence of minor alleles of 6 studied genes was associated with a significantly greater severity of the processes of pathological structural and functional remodeling of the heart. In particular, in this group of patients, compared with

dominant homozygotes, significantly higher volumes of the left chambers of the heart were noted (p <0.001, the reliability of intergroup differences for both indicators), a large value of the LV sphericity index (p <0.001). Also in this group of patients there was a higher index of impaired regional contractility (p <0.001), which corresponds to a greater number of coronary stenoses, and, accordingly, a lower ejection fraction (p <0.001) and an index of systolic myocardial remodeling (p <0.001). One of the characteristics of pathological remodeling was a significant increase in the LV myocardial mass index in the group of patients with minor alleles (p <0.001).

The functional state of the myocardium shows a more pronounced violation of diastolic relaxation (p <0.001) and a more pronounced violation of the effectiveness of the isometric functioning of the LV myocardium (Tei LV and total, p <0.001). A marked violation of the functional state of the left chambers of the heart led to higher levels of pressure in LA (systolic and jamming pressure in the pulmonary artery, p <0.001) in patients with minor alleles of the studied genes. In addition, in this group of patients, a more pronounced violation of the systolic function of the pancreas (TAPSE, p <0.001) was noted, with other parameters remaining structurally functional state of the right heart.

A more pronounced structural and functional myocardial remodeling, associated with the presence of minor alleles, led to a significant decrease in the distance traveled in TLC in this group of patients (p <0.001).

Stenting of the coronary arteries during the first year contributed to a statistically significant, but clinically insignificant, positive reverse myocardial remodeling, comparable in both groups, with the exception of 2 parameters: and the final LV diastolic volume in both groups of patients increased, which reflected the progression of pathological remodeling, more pronounced in the group of patients with a scoring of genetic polymorphism of the system of natriuretic peptides more than 6 (relative dynamics was 5.43 ± 9.56% versus 1.24 ± 7.44%, p <0.05). Another indicator, the dynamics of which differed in the groups identified by a point estimate of genetic polymorphism, is the index of violation of regional contractility. It decreased in both groups of patients, but to a greater extent in patients with a score of more than six, which is probably due to the large number of implanted stents (3.31 ± 1.02 versus 1.20 ± 0.28, p <0.001).

A comparative analysis of echocardiography of parameters one year after stenting of the coronary arteries in patients with angina pectoris of FC III-IV voltage depending on the presence of minor alleles demonstrated that significant differences remain between groups with more pronounced pathological structural and functional remodeling in the group of patients with minor alleles.

**Table 2. Comparative characteristics and annual dynamics of echocardiography characteristics in patients with angina pectoris of FC III-IV tension against the background of stenting of the coronary arteries depending on genetic polymorphism (numerator - patient indices - homozygotes for the dominant allele (n = 113) in the denominator - patients with minor alleles: heterozygotes or homozygotes for minor alleles (n = 45)**

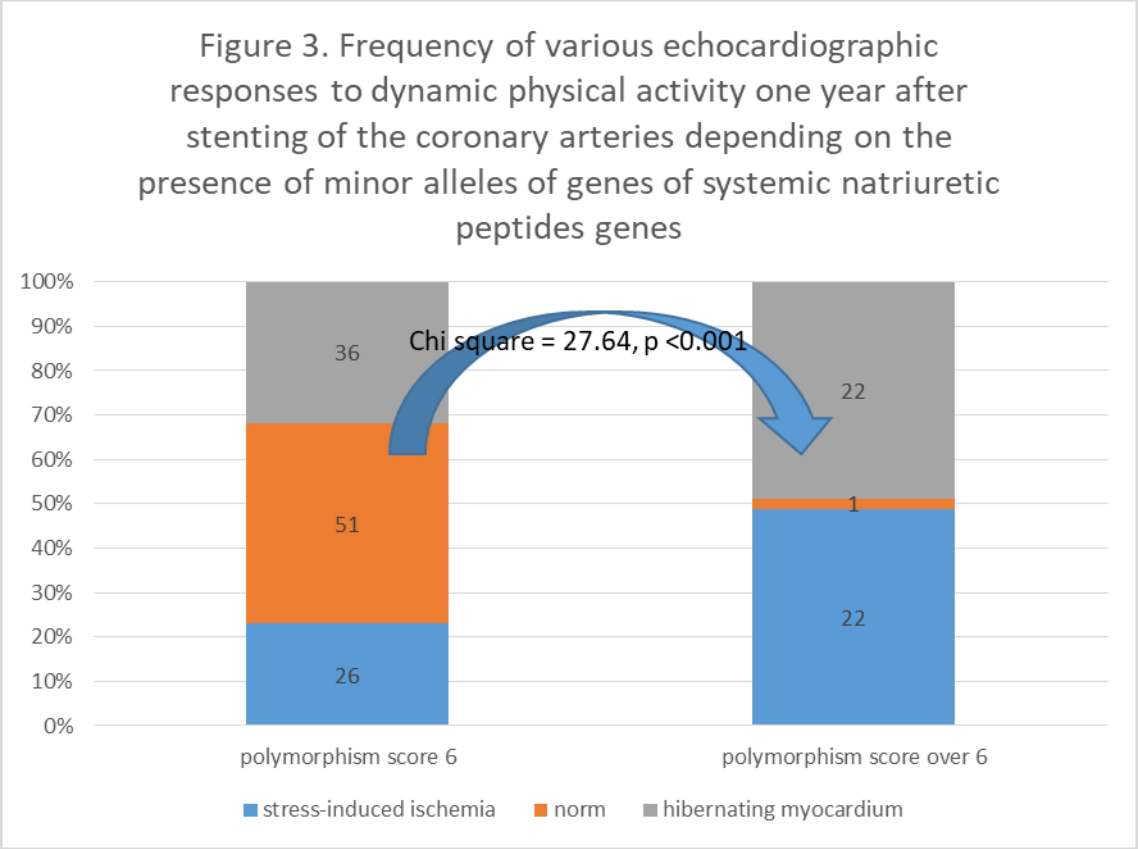
| Index | Initially | 12 months | Относительная динамика, % |
|---|---|---|---|
| The number of stenosis of the coronary arteries | 1,30±0,48<br>3,71±1,04^^^ | | |
| Age | 56,67±9,44<br>53,82±7,84 | | |
| Systolic blood pressure, mmHg | 137,17±24,79<br>143,78±31,93 | 128,98±17,31***<br>133,00±19,35** | -4,75±9,94<br>-5,70±10,11 |
| Diastolic blood pressure, mmHg | 88,32±16,47<br>92,00±20,95 | 82,74±11,74***<br>84,89±13,08*** | -5,02±10,30<br>-5,89±10,43 |
| Heart rate in minutes | 79,08±15,01<br>77,20±14,29 | 77,88±15,22<br>76,82±12,59 | -1,05±10,37<br>0,32±10,14 |
| Tshh, m | 461,87±56,86<br>255,29±54,65^^^ | 537,70±159,19***<br>280,53±88,19^^^* | 16,63±32,94<br>9,94±25,87 |
| ejection fraction,% | 57,31±3,51<br>47,53±2,56^^^ | 59,33±5,66***<br>51,00±6,31^^^** | 3,67±9,44<br>7,52±14,66 |

| | | | |
|---|---|---|---|
| ILP, ml / m2 | 27,39±4,20<br>47,20±6,84^^^ | 27,51±4,36<br>45,82±7,83^^^ | 0,52±5,53<br>-2,50±12,15 |
| final LV diastolic volume, ml / m2 | 95,39±8,99<br>120,22±12,49^^^ | 96,34±8,99<br>126,78±17,71^^^*** | 1,24±7,44<br>5,43±9,56^ |
| LV sphericity index, rel. | 0,76±0,12<br>1,18±0,27^^^ | 0,77±0,20<br>1,21±0,15^^^ | 0,42±16,98<br>5,39±17,42 |
| index of violation of regional contractility, score | 1,05±0,07<br>1,26±0,07^^^ | 1,04±0,06**<br>1,23±0,08^^^** | -0,84±3,21<br>-2,42±4,54^ |
| myocardial systolic remodeling index, units | 77,69±16,66<br>41,72±7,25^^^ | 82,01±21,73**<br>42,81±7,51^^^ | 5,69±18,60<br>7,09±41,61 |
| e'/a' ЛЖ, отн ед | 0,88±0,18<br>0,45±0,14^^^ | 0,90±0,18***<br>0,47±0,16^^^* | 3,11±7,77<br>4,78±14,31 |
| LV myocardial mass index, g / m2 | 119,44±9,44<br>151,53±16,32^^^ | 119,75±10,76<br>149,51±17,50^^^ | 0,30±5,05<br>-1,23±6,30 |
| Tei LV Rel. | 0,37±0,04<br>0,54±0,08^^^ | 0,35±0,06***<br>0,51±0,10^^^* | -5,06±10,98<br>-4,61±11,36 |
| Right ventricle, cm | 2,61±0,48<br>2,60±0,45 | 2,62±0,46<br>2,58±0,44 | 0,72±5,10<br>-0,54±2,20^ |
| TAPSE mm | 15,96±2,37<br>8,53±1,85^^^ | 16,57±2,67***<br>8,89±2,07^^^* | 3,90±8,83<br>4,54±10,99 |
| e '/ a' RV, rel. | 0,82±0,39<br>0,88±0,43 | 0,87±0,37**<br>0,90±0,38 | 13,15±43,70<br>12,61±51,90 |
| Jamming pressure in the pulmonary artery, mmHg | 16,49±2,08<br>24,49±2,90^^^ | 16,04±2,27***<br>23,91±3,10^^^** | -2,68±6,79<br>-2,37±4,94 |
| pulmonary systolic pressure, mmHg | 26,10±1,80<br>34,31±2,33^^^ | 25,65±2,22***<br>33,67±2,65^^^** | -1,73±4,50<br>-1,87±4,05 |
| Tei RV, отн ед | 0,38±0,10<br>0,39±0,10 | 0,37±0,10***<br>0,38±0,10* | -2,13±4,57<br>-2,63±5,89 |
| total Tei, rel | 0,75±0,10<br>0,93±0,12^^^ | 0,73±0,11***<br>0,89±0,14^^^** | -3,67±5,61<br>-3,83±8,04 |

Note: * - reliability and initial data, ^ - reliability of intergroup differences. One character - p <0.05, two characters - p <0.01, three characters - p <0.001.

Stress echocardiography at the end of the observation period revealed a significantly higher incidence of stress-induced ischemia in the group of patients with minor alleles (Fig. 3): 22 patients (48.89%) in the group of patients with a score of more than 6 and 26 patients (23.01 %) in the group with a score of 6 (chi square = 10.02, p <0.01). Interestingly, the phenomenon of hibernating myocardium was also more often detected in patients with minor alleles of the studied genes of the system of natriuretic peptides (22 patients - 48.89% versus 36 patients - 31.86%, chi square = 3.97, p <0.05) .

Thus, genetic analysis allows predicting the long-term effect of coronary artery stenting: the relative risk of progression of coronary artery disease (in the form of stress-induced ischemia) in patients with minor alleles is 2.12 times higher than in patients with dominant homozygotes for genes of the natriuretic peptide system.




In the course of the study, a correlation analysis of the interconnections of the point estimate of polymorphism according to the proposed scale and the echocardiography parameters at the end and at the end of the observation period was carried out (Table 3). Significant relationships were found between the number of minor alleles and the severity of pathological remodeling of the heart, namely the volumes of the left chambers of the heart, ejection fraction, index of impaired regional contractility, index of systolic myocardial remodeling, sphericity index, impaired LV diastolic function, integral LV myocardial functioning index, myocardial mass index LV, TAPSE, and pulmonary pressure ($p < 0.01$ for all correlation coefficients with baseline data and rates at the end of the first year of observation). These relationships are understandable given the above differences between patients with and without minor alleles. A study of the relationship between the relative dynamics of the echocardiography and the scoring of genetic polymorphism revealed significant positive relationships with the dynamics and the final LV diastolic volume and ejection fraction ($p < 0.05$ for both correlation coefficients).

**Table 3. Correlation coefficients of echocardiography and their dynamics during the year after stenting the coronary arteries with a genetic polymorphism score (critical values of the correlation coefficient for n> 100: 0.195 for a confidence level p <0.05, 0.254 for a confidence level p <0.01)**

| Indicators | Initially | 12 months | Относительная динамика |
|---|---|---|---|
| Systolic blood pressure, mmHg | 0,041117 | 0,045204 | -0,0007 |
| Diastolic blood pressure, mmHg | 0,024314 | 0,019784 | -0,00316 |
| Heart rate in minutes | -0,04762 | -0,02748 | 0,042303 |
| Tshh, m | -0,84644** | -0,62298** | -0,11026 |
| ejection fraction,% | -0,80534** | -0,48613** | 0,236834* |
| ILP, ml / m2 | 0,874804** | 0,838236** | -0,15987 |

| | | | |
|---|---|---|---|
| final diastolic LV volume, ml / m2 | 0,813246** | 0,811696** | 0,220587* |
| LV sphericity ind, rel. | 0,746204** | 0,671425** | 0,049146 |
| index of violation of regional contractility, score | 0,833982** | 0,805216** | -0,1888 |
| myocardial systolic remodeling index, units | -0,70807** | -0,61654** | 0,127818 |
| e '/ a' LV, rel. | -0,77774** | -0,77432** | 0,037537 |
| LV myocardial mass index, g / m2 | 0,852533** | 0,81017** | -0,08925 |
| Tei LV Rel. | 0,881372** | 0,786446** | 0,027374 |
| Right ventricle, cm | -0,0308 | -0,05444 | -0,10649 |
| TAPSE mm | -0,81285** | -0,78713** | 0,052449 |
| e '/ a' RV, rel. | -0,01939 | -0,04572 | -0,01068 |
| Jamming pressure in the pulmonary artery, mmHg | 0,863524** | 0,848759** | 0,045974 |
| систолическое давление в легочной артерии , мм.рт.ст | 0,864744** | 0,830257** | 0,010131 |
| Tei RV, отн ед | 0,004744 | 0,001361 | -0,03104 |
| total Tei, rel | 0,620695** | 0,580541** | -0,00357 |

Note: * - reliability of the correlation coefficient. One character is p <0.05, two characters are p <0.01.

## CONCLUSION

The present study found that the presence of minor alleles of genes of the system of natriuretic peptides is associated with a greater prevalence of atherosclerotic lesions of the coronary bed, the activity of structural and functional remodeling of the heart. In addition, the presence of minor alleles reduces the long-term effectiveness of coronary revascularization, both in the aspect of coronary atherosclerosis and in the aspect of the functional state of the myocardium (progression of LV dilatation and preservation of the hibernating myocardium).

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